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WPI Abstract Accession No. 84-291650/47 & JP59/179877 A WPI Abstract Accession No. 84-266835/43 & JP59/163474 A

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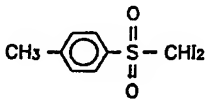
(54) Germicidal composition and soap

(57) A germicidal composition comprises diiodomethyl-p-tolyl sulfone (I), and 5-amino-1,3-bis(2-ethylhexyl)-5-methyl-hexahydropyrimidine (II) and/or a salt III selected from the group consisting of chlorhexidine diacetate, chlorhexidine digluconate or chlorhexidine dihydrochloride in a suitable organic solvent.

A germicidal soap containing the compound I and at least one or both of the compounds II and III is also disclosed.

The germicidal composition and soap are capable of preventing the contamination of daily goods and protecting human bodies from infectious or pathogenic microorganisms, and are also effective in the sterilization and treatment of an infected part.

The composition is effective for various groups of microorganisms (including eucaryotic cells and procaryotic cells) and is safe to human bodies, animals and plants.



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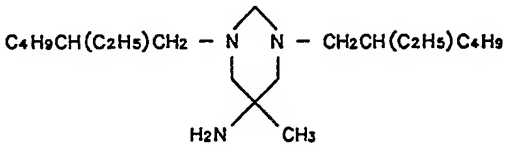

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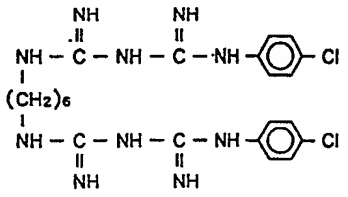

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GERMICIDAL COMPOSITION AND SOAP CONTAINING THE SAME

BACKGROUND OF THE INVENTION

Field of the invention

The present invention relates in general to a germicidal composition and a soap containing the same, and more particularly to a composition having a variety of sterilizing spectra, harmless to human body and a soap containing the same, capable of inhibiting the growth of microorganisms which are parasitic on the skin to cause a variety of cutaneous diseases and sterilizing the parasites.

Description of the Prior Art

Microorganisms, by definition, are called organisms that are too small to be perceived clearly by the unaided human eye. They are able to grow and reproduce for themselves under suitable conditions such as nutrients, humidity, temperature and the like. Microorganisms have a wide taxonomic distribution; they include some metazoan animals, protozoa, many algae and fungi, bacteria, and viruses.

Such microorganisms always exist all around, for example, in the human skin and even where the magma erupts. They play important roles in circulating matters in the ecosystem. In addition, they are utilized in industrially important

processes, such as the production of critical medicines, foods and the like. However, some microorganisms may infect humans, animals or plants to cause a variety of diseases therein. Other microorganisms may putrefy lumber, paper, cloth, food, etc., so that the quality of life environment is deteriorated.

On human skin, microorganisms inhabit in the quantity of approximately 10^4 colony forming units (hereinafter "cfu") per 1 cm^2 of the skin. This group of microorganisms is called a normal flora, which is harmless to the human body. Rather, it is advantageous, since it prevents the skin from being infected by other harmful microorganisms. The number of normal flora is maintained constant by the correlation of the bacteriolytic properties of hydrolytic enzymes (e.g. lysozymes) which are widespread in biological tissues and secretions, the transferin which is also a kind of secretions, and the metabolites of the microorganisms themselves. However, if a human body comes to be weak in his or her immune system or comes in contact with a contaminated substance, particular pathogenic microorganisms propagate abnormally, so that he or she becomes ill with bacterial or fungal diseases. The lumber, cloth, paper, food and etc., which are founded easily in daily life, may provide ideal inhabitats to microorganisms and thence are often contaminated with them. Moreover, in extreme condition such as nutrient limitation, high temperature, dry condition and the like, microorganisms

can produce microscopically distinguishable resting bodies (endospores) which are highly resistant to heat and dry condition, so that they survive until the extreme environment is improved. Accordingly, there always exists a possibility such that human body is infected with the microorganisms through contaminated floor, cloth, wallpaper, dish towel or food.

It is known that a substantial part of infected skin diseases (in USA, 5 to 10 % of total hospital patients) are acquired through a public health institute such as a hospital (hospital-acquired infection). It is believed that the diseases propagate among patients, utilizing the medical personnels and instruments which are always in contact with the patients as carriers. Furthermore, the patient who becomes to have a weakened immune function caused by administration of drugs or surgery and thus is badly resistant to the infection develops to a very serious state.

In an effort to solve the problems, a germicidal cleanser of a form of an ointment or a soap is suggested in Korean Patent Publication No. 90-2935. However, the cleanser's sterilizing ability is doubtful. In addition, until now, there has not been developed a germicidal material which is utilized easily at any time, regardless of place.

According to the requirement, it is necessary to develop a germicidal composition, which is capable of the preventing

contamination of daily goods and protecting human bodies from being infected with the infectious microorganisms, and which is further effective in sterilization and treatment for an infected part and is safe to human bodies, animals and plants.

In developing a germicidal substance, difficulties encountered are the diversity of microorganisms and the safety to human body.

There is recognized a profoundly important dichotomy among the various groups of microorganisms with respect to the internal architecture of the cell. Two radically different kinds of cells exist in the contemporary living world. The more complex eucaryotic cell is the unit of structure in metazoan animals, protozoa, fungi, and all save one of the groups that had traditionally been assigned to the algae. The less complex procaryotic cell is the unit of structure in two microbial groups; the eubacteria and the archaebacteria. Of the procaryotes, the eubacteria can be subdivided into Gram-negative eubacteria and Gram-positive eubacteria on the basis of the structure of the cell wall. In general, microorganisms diversely response to germicidal substances. A germicidal substance is often ineffective to the Gram-negative bacteria even though it kills the Gram-positive bacteria. Moreover, it is common that a substance with a potent sterilizing power for both the Gram-positive and Gram-negative bacteria is incapacitated for the eucaryotic microorganisms such as yeasts

and fungi.

SUMMARY OF THE INVENTION

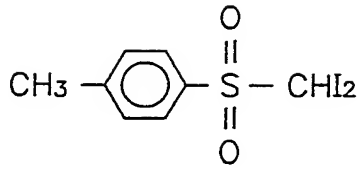
For solving the aforementioned problems, the inventors have recognized that there exists a need for a germicidal composition, effective for a wide extent of microorganisms, which is capable of inhibiting the growth of microorganisms or sterilizing them and is safe to human bodies, animals and plants, and for an easily usable form of a material including the germicidal composition at any time, regardless of place.

Accordingly, in an aspect of the present invention, there is provided a germicidal composition which is capable of sterilizing microorganisms over various groups.

According to another aspect of the present invention, there is provided a germicidal composition which is safe to human body and other living bodies such as animals and plants.

According to a further aspect of the present invention, there is provided a soap which has an excellent inhibitory effect and disinfecting power for microorganisms.

The above objects are accomplished by providing a composition which comprise a compound represented by the following formula I;



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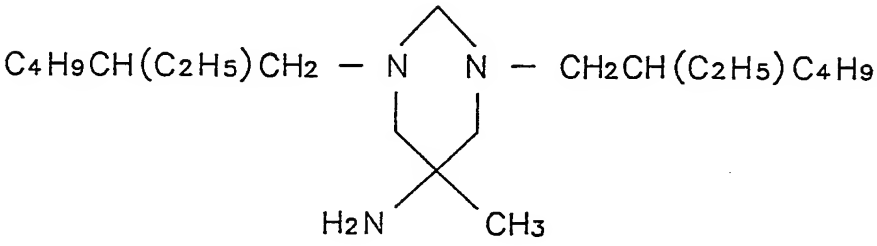
at least one or both of compounds represented by the following formulas II and III



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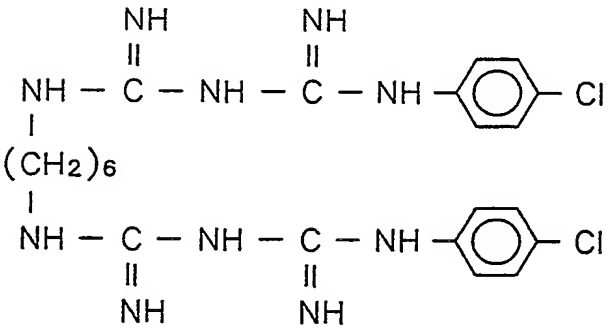


, R [III]

wherein R is selected from the group consisting of diacetate, digluconate and dihydrochloride; and

a solvent.

The compounds of the above formulas I, II and III are known to be harmless to human body.

These and other objects together with others not

specifically mentioned will become clear to those skilled in the art as the following description proceeds.

DETAILED DESCRIPTION OF THE INVENTION

Hereinafter, the present invention will be described in detail.

Used as an ingredient of the inventive germicidal composition, diiodomethyl-p-tolyl sulfone represented by the formula I has a potent germicidal power for Gram-positive bacteria, yeasts and fungi, but is little effective to Gram-negative. Another potent ingredient represented by the formula II, 5-amino-1,3-bis(2-ethylhexyl)-5-methyl-hexahydropyrimidine is capacitated to disinfect Gram-negative bacteria. The other compound represented by the formula III, which is selected from chlorhexidine (1,1'-hexamethylene-bis[5-(4-chlorophenyl)biguanide]) diacetate, chlorhexidine digluconate or chlorhexidine dihydrochloride, is effectual to Gram-negative bacteria and is superior to the compound of the formula II in disinfecting Gram-positive and fungi.

In accordance with the present invention, the germicidal composition is prepared by combining the diiodomethyl-p-tolyl sulfone of the formula I with the 5-amino-1,3-bis(2-ethylhexyl)-5-methyl-hexahydropyrimidine of formula II and/or the compound of the formula III, whereby the composition can

disinfect Gram-positive and Gram-negative bacteria as well as the eucaryotes such as yeasts and fungi.

For example, the composition according to the present invention is effective to bacteria such as Bacillus subtilis, Escherichia coli, Klebsiella pneumonia, Micrococcus multicida, Mycobacterium tuberculosis, Proteus vulgaris, Shiegella dysenteria, Staphylococcus aureus, Staphylococcus epidermis, Streptococcus faecalis and the like. The inventive germicidal composition inhibits the growth of yeasts or fungi, such as Aspergillus sp., Aerobacidium pullulans, Candida sp., Epidermophyton sp., Fusarium sp., Microsporum sp., Malassezia furfur, Penicillium citrinum, Trichophyton sp., and like.

The composition ratio of the ingredients is preferably on the order of 1:1 weight ratio in case that the germicidal composition comprises of the compounds of the formulas I and II or the compounds of the formulas I and III. In the meanwhile, the composition ratio is preferably on the order of 1:1:1 weight ratio in case that the germicidal composition comprised of all the compounds of the formulas I, II and III.

Preferred solvent to be used in the present invention is alcohols and more preferably ethanol.

According to the present invention, the germicidal composition may be changed into a useful form including various other materials. For example, the inventive germicidal composition may be admixed with soap base in order

to manufacture a soap as described later. The germicidal composition according to the present invention may be also added into an organic solvent such as ethanol in order to prepare an effectual sterilizing solution for surgery. The germicidal composition and the soap including the same have an admirable effect in inhibiting the growth of microorganisms, so that may be utilized for cleaning or sterilizing hard parts of household goods, such as wall, floor, table, article of plastics and the like, or for laundering clothes to sterilize them.

Particularly, the germicidal composition and the germicidal soap according to the present invention have a remarkable disinfecting power to yeasts and antrophylic fungi which are strongly penetrative into human body, such as Candida albicans, Trichophyton mentagrophytes, and Epidermophyton floccosum. These exemplary microorganisms cause fungus-type skin diseases such as eczematosis, dermatophytosis, trichophytia and the like.

EXAMPLE 1

Preparation of Germicidal Composition.

First, 20 g of diiodomethyl-p-tolyl sulfone was dissolved in 1,980 ml of 99 % pure ethanol. Into the solution, 20 g of 5-amino-1,3-bis(2-ethylhexyl)-5-methyl-hexahydropyrimidine and 20 g of chlorhexidine digluconate were added, and were stirred

vigorously for 5 minutes to prepare a germicidal composition.

The prepared composition contained the three effective ingredients of 20,000 ppm, respectively.

It is apparent that the concentration of the effective ingredients and the ratio thereof may vary in dependence with the purpose intended.

EXAMPLE 2

The growth inhibitory effects of the composition prepared in the Example 1 were measured for a variety of microorganisms. Herein, the growth inhibitory effect was said to be the value of minimal inhibitory concentration (hereinafter "MIC") of germicidal composition, which was determined by inoculating the definite number of microorganisms in suitable culture media containing various concentrations of the germicidal compositions, respectively, culturing the microorganisms at a constant temperature for a time and selecting the medium with a minimal concentration of the composition in which the microorganisms was not able to grow.

The culture composition for the growth of microorganisms was as shown in the following Tables 1 and 2.

Table 1

Medium for the growth of Bacteria.

Yeast Extract	3 g
Trypton	5 g
Glucose	1 g
Distilled Water	1 l (pH 5.6)

Table 2

Medium for the growth of Fungi.

Malt Extract	40 g
Peptone	10 g
Chloramphenicol	10 mg
Distilled Water	1 l (pH 5.6)

* when preparing a plate culture, agar was added in an amount of 1.5 %

The medium components were sterilized at 121 °C for 15 minutes according to a conventional method to be used.

A stock solution for the microorganisms was prepared as follows: plate cultures were seeded by picking up a minute quantity of bacteria and yeasts cells on a platinum needle, previously sterilized by passing through a flame, and drawing it several times rapidly and lightly across the surfaces of

the cultures according to the conventional streaking method; the microorganisms were cultured at 30 °C for 2 to 3 days to develop into isolated colonies; the microorganism cells on the isolated colonies were picked up on a loop and were suspended in 0.9 % NaCl solution (hereinafter, "physiological saline solution"). In case of fungi, they were incubated on a plate culture at 30 °C for 5 to 7 days to form spores. Into the plate culture, 10 ml of a physiological saline solution containing about 5 % by weight of Tween 80 was poured and then a spore suspension was prepared by scraping the culture surface with the loop.

The stock solution thus prepared was measured to count the total number of microorganisms included therein, in a conventional manner and then, was inoculated in liquid cultures containing various concentrations of the germicidal compositions, respectively. The size of inoculum had to be maintained 10^4 cfu/ml. After inoculating, the culture vessel was rotated in a speed of 150 rpm at 30 °C. After 48 hours for bacteria, or 72 hours for fungi, the growth was investigated to determine MICs.

The results of the germicidal composition of Example 1 for each groups of microorganisms are given as shown in the following table 3.

EXAMPLE 3

The sterilizing effects of the germicidal composition prepared in Example 1 were measured for various microorganisms. Herein, the sterilizing effect was said to be the value of minimal biocidal concentration (hereinafter "MBC") of the germicidal composition, which was determined by inoculating the definite number of microorganisms in suitable culture media containing various concentrations of the germicidal compositions, respectively, incubating the microorganisms for some time and selecting the medium with a minimal concentration of the composition in which the number of the cultured microorganisms became less than 0.1 % of that in the inoculum. In the conventional total viable cell count method, the value was determined by performing the experiment of Example 2 and measuring the number of residual microorganisms which were survived in culture media wherein microorganisms were unable to grow.

The results of the germicidal composition of Example 1 for each group of microorganisms are given as shown in the following Table 3.

Table 3

MIC and MBC of the germicidal composition for microorganisms.

Microorganisms	MIC(ppm)	MBC(ppm)
· Bacteria		
Bacillus subtilis	50	50
Escherichia coli	100	200
Mycobacterium tuberculosis	250	500
Staphylococcus aureus	200	300
Streptococcus faecalis	200	300
· Yeasts		
Candida albicans	100	200
· Fungi		
Aspergillus sp.	38	75
Epidermophyton sp.	38	75
Trichophyton sp.	38	75

EXAMPLE 4

Manufacture of germicidal soap

It is important to know the dilution degree of each constituents consisting of the soap when the soap is used, since the concentrations of each constituents are to be determined In order to manufacture a soap. Herein, there was referred a method which was disclosed in European Patent No. 0 363 215 (A2), which analyzed the influence of constituents into the properties of the soap. That is, it was assumed that the constituents of soap was diluted 100 times when the soap

was used.

The germicidal composition of Example 1 was added in a concentration of not less than 25 % to manufacture a soap which had a potent sterilizing power to all microorganisms shown in the above Table 3.

The composition of soap was as follows:

· Soap base or Neat soap	97.5 g
· The germicidal composition	25.0 ml
· Other additives	
Perfume	1.5 ml
Pigment	0.01 g

The soap base was subjected to the treatment of milling for 5 minutes to pulverize it completely. With stirring the pulverized, the germicidal composition and the other additives were added. The resulting mixture was dried to vaporize ethanol completely and to make the water content less than 5 %. The dried mixture was again subjected to milling for 15 minutes to mix the added constituents completely. Maintaining the temperature in 32 to 37 °C, the mixture was plodded in a Stephen Beck plodder, followed by the injection of a form of ribbon. Using a midget multipress, the injected mixture was pressed to form a suitable shape of soap.

On manufacturing a germicidal soap, each effective ingredient may be incorporated in a concentration of 0.5 %,

based on the weight of soap base, instead of using the ethanol solution containing the effective ingredients.

EXAMPLE 5

The growth inhibitory effects of the germicidal soap manufactured in Example 4 were measured for various microorganisms. Herein, the growth inhibitory effect is represented by growth inhibitory degree (%) which means a relative extent in that the aqueous solution of soap containing the germicidal composition inhibits the growth of microorganism, as compared with the aqueous solution of soap without the germicidal composition.

The growth inhibitory effect was determined as follows: 0.5 ml of stock solution containing various microorganisms in the quantity of 1,000 cfu/ml was admixed with 2 % soap solution (a suspension containing 2 g of soap and 100 ml of sterilized, distilled water) and then, the resulting solution was poured into a plate culture and was incubated at 30 °C for 48 hours for bacteria or for 72 hours for yeasts and fungi to develop into colonies. The numbers of colonies on the culture were counted to compare the treatment with the soap containing the germicidal composition with the soap without the germicidal composition.

The results are given as shown in Table 4.

Table 4

Growth inhibitory effect of germicidal soap for microorganisms

soap	Staphylococcus aureus		Candida albicans		Trichophyton sp.	
	survival no (cfu)	IR* (%)	survival no (cfu)	IR (%)	survival no (cfu)	IR (%)
A	1200	-	760	-	1,070	-
B	0	100	4	99	0	100

* Growth Inhibitory rate

** A: not including the germicidal ingredients
B: prepared according to Example 4

EXAMPLE 6

The sterilizing effects of the soap manufactured in Example 4 were measured for various microorganisms. Herein, the sterilizing effect is represented by sterilizing rate (%) which means a relative extent in that the aqueous solution of soap containing the germicidal composition inhibits the growth of microorganism, as compared with the aqueous solution of soap without the germicidal composition.

The sterilizing effects were determined as follows: 0.5 ml of stock solution containing various microorganisms in the quantity of 1,000 cfu/ml was admixed with 0.5 ml of 2 % soap solution (a suspension containing 2 g of soap and 100 ml of sterilized, distilled water) in a microcentrifuge tube and left at 30 °C for 10 minutes; microorganisms were inoculated

to the soap solution and then, centrifuged at a speed of 8,000 rpm for 5 minutes; the supernatant was removed carefully; 1 ml of physiological saline solution was poured into the residual precipitated microorganisms to wash the soap solution; the last step was repeated 2 to 3 times and then 1 ml of physiological saline solution was poured into the residual precipitated microorganisms; the resulting solution was poured in a plate culture, which was subsequently incubated at 30 °C for 48 hours for bacteria and for 72 hours for yeasts and fungi. The numbers of colonies on each culture were counted to compare the treatment with the soap containing the germicidal composition with the soap without the germicidal composition.

The results are given as shown in Table 5.

Table 5

Sterilizing effect of germicidal soap for microorganisms

soap	Staphylococcus aureus		Candida albicans		Trichophyton sp.	
	survival no (cfu)	SR* (%)	survival no (cfu)	SR (%)	survival no (cfu)	SR (%)
A	700	-	825	-	730	-
B	7	99	8	99	204	72

* Sterilizing rate
** A: not including the germicidal ingredients
←B: prepared according to Example 4

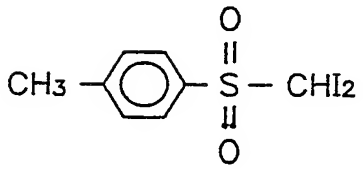
As apparent from the above examples, it is expected that the germicidal composition and the soap containing the same according to the present invention are capable of preventing the skin from being infected by harmful microorganisms as well as curing the previously infected regions.

Whilst the present invention has been described with reference to certain preferred embodiments and examples, it will be appreciated by those skilled in the art that numerous variations and modifications are possible without departing from the spirit or scope of the invention as broadly described.

WHAT IS CLAIMED IS:

1. A germicidal composition, which comprises of:

a compound represented by the following formula I;



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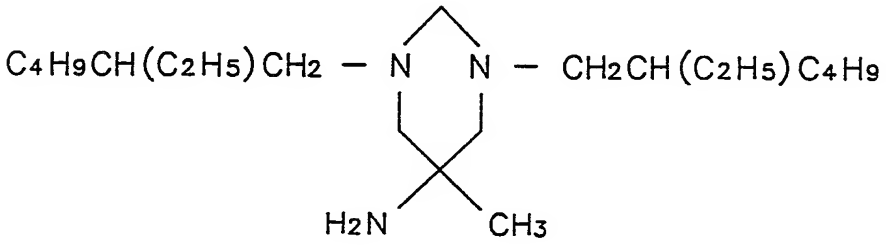
at least one or both of the compounds represented by the following formulas II and III



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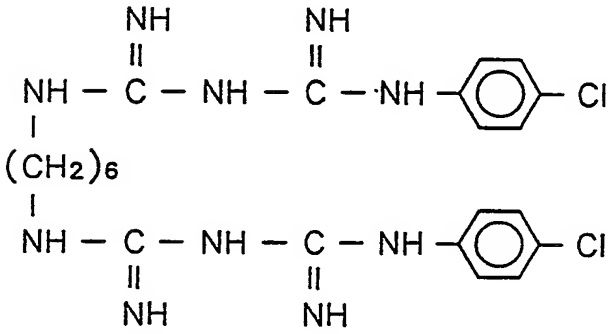


, R

[III]

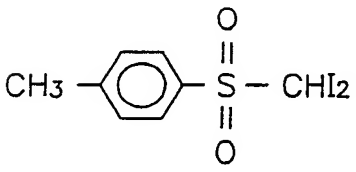
wherein R is selected from the group consisting of diacetate, digluconate and dihydrochloride; and

a solvent capable of dissolving said compounds.

2. A germicidal composition according to Claim 1, in which said solvent is alcohol.

3. A germicidal composition according to Claim 1, in which said compound of formula I and said compound of formula II or III are added in a weight ratio of 1:1, or said compound of formulas I, II and III are added in a weight ratio of 1:1:1.

4. A germicidal soap, comprising a composition which comprises of: a compound represented by the following formula I; and



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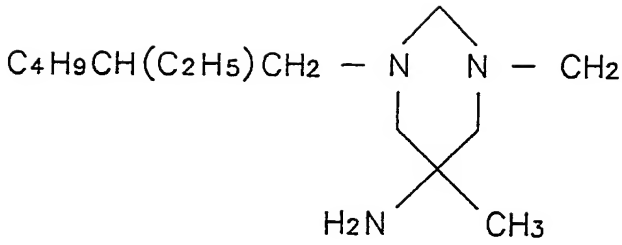
at least one or both of compounds represented by the following formulas II and III



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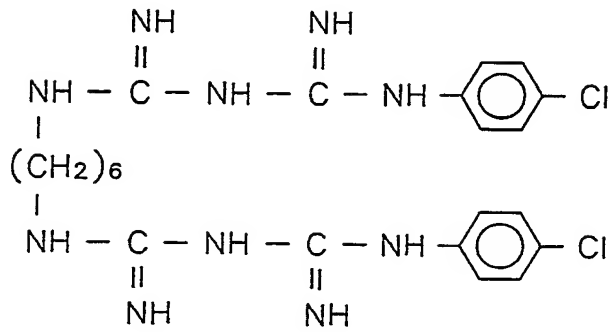

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wherein R is selected from the group consisting of diacetate, digluconate and dihydrochloride.

5. A germicidal soap according to claim 4, in which the composition is directly added to a soap base.

6. A germicidal soap according to Claim 4, in which the composition is dissolved in an alcohol to be added to a soap base.

7. A germicidal soap according to Claim 6, in which the alcohol is ethanol.

Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

Application number
GB 9321537.4

Relevant Technical Fields

(i) UK Cl (Ed.L) A5E (EBB); C5D (DEA)

(ii) Int Cl (Ed.5) A01N 47/00; C11D

Search Examiner
S J QUICK

Date of completion of Search
21 DECEMBER 1993

Databases (see below)

Documents considered relevant following a search in respect of Claims :-
1-7

ONLINE DATABASE: CAS ONLINE; CHEMICAL ABSTRACTS FORMULA INDEX 1920-1956

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
A	WPI Abstract Accession No 84-291650/47 and JP 59/179877 A (ASAHI CHEMICAL IND) 12.10.84, see abstract	
A	WPI Abstract Accession No. 84-266835/43 and JP 59/162474 A (ASAHI CHEMICAL IND) 14.09.84 see abstract	

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